REMARKS

Claim Amendments

Claims 1, 2, 4, 6, 8, 9 and 14-16 are present in the application. Claims 3, 5, 7, and 10-13 are canceled. Claims 6, 8, 9 and 14-16 are now withdrawn. Claims 1, 2, and 4 are subject to examination.

Restriction and Election

Applicant acknowledges that the Examiner has made final the restriction requirement. Claims 6, 8, 9 and 14-16 have now been withdrawn but may be subject to rejoinder for further examination if claims 1, 2 and 4 are found allowable.

Incorporation of Foreign Priority Claim

The Examiner continues to deny the foreign priority claim to PZ2003000002 on the basis that Applicant has not listed the priority claim in the first sentence of the specification or in an ADS, citing as authority MPEP 201.11.

Again, Applicant respectfully traverses.

Respectfully, Applicant points out that MPEP 201.11 relates to claims of priority to prior filed applications under 35 U.S.C. 120 and 119(e), including continuation, divisional and PCT applications, and provisional applications. The Examiner is looking at the wrong rule.

The claiming of priority to foreign applications under 35 USC 119 (a-d) and (f) is instead covered under MPEP 201.13, which expressly states that:

> A priority claim need not be in any special form and may be a statement signed by a registered attorney or agent. A priority claim can be made on filing: (A) by including a copy of an unexecuted or executed oath or declaration specifying a foreign priority claim (see 37 CFR 1.63(c)(2)); or (B) by submitting an application data sheet specifying a foreign priority claim (see **37 CFR 1.76**). (emphasis added)

Applicant has clearly disclosed the foreign priority claim in the Declaration executed and submitted by the Applicant, and therefore is in total compliance with the MPEP, the Rules, and the Law for the claiming of foreign priority to PZ2003000002.

Claim rejection under 35 USC §103(a)

Claims 1, 2, and 4 are rejected as obvious over Caputo (US2002/065421 or the "421 application") in view of Takashima et al (US2002/0051926 or the "926 application"), and Stavrianopolous et al (US2003/0225247 or "247 application").

The Examiner in the present Final Action maintains the prior rejection

Applicant again respectfully traverses.

The compounds of present (and past) Claim 1 have two essential features: (1) they comprise always two functionalized linkers (i.e. having a terminal functional group capable of reacting) on the two indolenine ammonium atoms: R_1 and R_2 and (2) one of these linker is always functionalized with an alkyne group: -C≡CH.

While the Examiner asserts that the proviso at the end of claim 1 does not exclude that the compound of formula 4a in US '421 may have the identified moiety "-R_8-Y" attached to the indole ring, it is incorrect to say that the claim is made obvious in view thereof. First of all, none of the disclosed compounds in US '421 contains at the same time two functionalized linkers in the positions corresponding to R_1 and R_2 of the present Claim 1. Second, none of the disclosed US '421 compounds contain one linker, in a position corresponding to either R_1 or R_2, that is functionalized with a -C≡CH group.

US '421 claims and describes asymmetrical indocyanines compounds having always only a single functionalized linker, which therefore is capable of bonding only one molecule (either a biomolecule or a dye). If one looks in US '421 at formula (I) of claim 10, or at any one of the compounds of claim 11, or at any one of the compounds of claim 14, or even at any one of the compounds illustrated in figures 4 to 11, one realizes immediately that when one substituent on either of the two indolenine ammonium atoms is functionalized, the other is not functionalized: namely it is a simple ethyl group (-CH_2-CH_3), which is well known to be inert.

Moreover, when one functionalized linker is present on the benzyl ring of one of the indolenine moiety, then neither of the two indolenine ammonium atoms, corresponding to the present R_1 and R_2 positions, is functionalized, both bearing an inert ethyl group.

The Examiner also contests Applicant's argument that the '421 application teaches away, by questioning "First, if a compound with 'carboxylalkyl or sulfonatoalkyl chains or electron withdrawing groups in the benzene ring' would decrease the reactivity of the indolenines, why

the instant application claims the such less active compound as the Formula (Ic) in claim 4 for the same application?"

It should be clarified that the issue of reactivity of the indolenine moiety pertains to the synthesis reaction of the compound, and not to the reactivity of the linkers to biomolecule or a second dye molecule. This synthesis reactivity was relevant in US '421 for the simple reason that the '421 application relates to asymmetric indocyanine dyes (see for example claim 14). Since the final molecule is obtained by reacting a first indocyanine moiety with a second different indocyanine moiety, if the reactivity of the two is different, the synthesized amount of the desired asymmetrical indocyanines "heterodimer" is much lower than the amount of the symmetrical "homodimer". For this reason, selection of the chains or electron withdrawing groups in the benzene ring became a relevant concern in the '421 application.

These considerations are completely irrelevant in the present case since the claimed indocyanine dye is symmetrical. Therefore the synthesis reactivity aspect is less relevant or irrelevant.

Likewise, all of the compounds disclosed in the description, claims and figures of the US '247 and the US '926 references are "monofunctional" having only one linker, or in the case of the US '926 reference, two identical functionalized linkers. One cyanine molecule can react with one biomolecule only. This is evident for example from paragraph [0135] of the US '247 reference where it is clarified that "*R_1-R_8 comprises a reactive group that could be used to join the cyanine dye to a desired target molecule*". There is no express or inherent description or suggestion of joining the cyanine dye to two desired target molecules.

Therefore the skilled person could not find in either US '247 or US '926 any express teaching, suggestion or motivation to produce a cyanine modified compound as claimed in present claim 1 usable as a bridge between two biomolecules, or between a biomolecule and a second dye molecule.

The Examiner also states that both the US '247 and US '926 teach a cyanine compound that has an alkyne (-R1≡CH) attaching to the cyanine core moiety, used as a dye and a probe for labeling biomolecules, respectively. Applicants disagree. Literally, both the US '247 and US '926 teach a substituent "R" which can be selected from a group of substituents, one of which may be alkyne. The Examiner has not disclosed a motivation within the references for one to

select the alkyne substituent from among the several other substituents in the group, nor is the selection of the alkyne moiety "obvious to try".

Consequently, the Examiner has failed to establish a *prima facie* case of obviousness, or in the alternative has failed to rebut Applicants' traversal of the same.

Therefore, the compounds of claim 1, 2 and 4 are patentably distinct from the compound of US '421, further in view of the '926 application and the '247 application.

Double patenting

The Examiner has rejected claims 1, 2, and 4 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-11 of US Patent 6,136,612 (the '612 patent).

Applicant traverses.

Present Claim 1 necessarily requires, as an essential feature, that the two linkers in R_1 and R_2 be functionalized by different reacting groups: the former being always R_1-C≡CH, the latter never comprising the alkyne group (-C≡CH). Accordingly, the two linkers have different reactivity.

Actually, it is specifically indicated in paragraph [0012] of the present application that when more than one functionalized linker is present, undesired cross-linking between multiple similar molecules, undesired multiple reactions or purification problems occur.

Since the aim of the molecules of Claim 1 is to link two different ligand-molecules (either two different biomolecules or a biomolecule and a second dye), the presence of two different functionalized linkers avoids the above indicated problems.

In fact having different reactivity, it is always possible to select operating conditions suitable for reacting the first biomolecule (or dye) with the most reactive linker, while leaving the second linker available for the second subsequent reaction with the second biomolecule (or dye). This avoids obtaining two identical biomolecules bonded to the same cyanine compound of Claim 1.

US '612 discloses indocyanine fluorescent dyes comprising two functionalized linkers in position R_1 and R_2. As immediately evident, the two linkers are always disclosed as being functionalized with the same, identical reacting group, one selected from "-COOH, phthalimido",

etc. See, by example, claims 1, 7 to 11 and columns 7, 12, and 14.

If the person ordinarily skilled in the art wished to improve the availability of the reacting groups, and if he/she, as alleged, found in US '926 a suggestion to use an alkyne group, such as -C≡CH, nevertheless, by following the teaching in the US '926 reference, he/she would have envisaged cyanine molecules always comprising two identical linkers. In fact US '926 (as does US '612) discloses indocyanine molecules having either two identical functionalized linkers or only one functionalized linker. See paragraph [0084] and the compounds on pages 7, 8, 9 and 10, and in Claims 1 and 2. In other words, the skilled person would not have found in US '926 any motivation or reason to use two differently functionalized linkers.

Also US '247 discloses, among many various other possible substituents, linkers functionalized with an alkyne group, namely -C≡CH. Yet US '247 discloses molecules having only one linker. Therefore, if the one of ordinarily skill would have perhaps found in this document some hint to use a -C≡CH functional group, he/she would not have found in this document any motivation to have two different functional linkers.

In conclusion, the Examiner has failed to establish a *prima facie* case of obviousness in view of US '612, or in the alternative, the Examiner has failed to rebut Applicants' traversal of the same.

Therefore, the compounds of claim 1, 2 and 4 are patentably distinct from the compound of US '612, further in combination with US '926 or US '247.

Claim objections

The Examiner had objected to Claims 1, 2, and 4 as containing both elected and non-elected subject matter.

Applicant understands that, should the elected subject matter be allowed, the Examiner would extend examination to the non-elected embodiments contained in New Group II. In view of the present amendments and arguments, the elected subject matter appears to be patentable over the prior art of record, and Applicant requests that the remaining non-elected subject matter of the claims be examined.

CONCLUSION

Applicant believes a full and complete response to the Final Action has been made. In view of the above remarks that traverse the rejections, allowance of all the claims is respectfully requested.

Respectfully submitted,

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